REMARKS / ARGUMENTS

Claims Pending

Claims 1-15 were pending. Claims 2-5, 7 and 11-15 have been cancelled. Accordingly, claims 1, 6 and 8-10 are now pending.

Claim Objections

The objection to claim 3 is rendered moot by its cancellation.

Claim Rejections – 35 USC § 112

Claims 1 stands rejected under 35 USC 112, first paragraph. The action is understood as conceding that the specification does enable the use of ritonavir (as the inhibitor of CYP 450) in combination with the compound of formula I, while asserting that the specification does not enable the use of other CYP 450 inhibitors. To overcome the rejection of claim 1 under 35 USC 112, first paragraph, the claim has been amended by replacing the phrase "one or more inhibitors of CYP 450" with -- ritonavir --.

Claim 1 has also been rejected under 35 USC 112, second paragraph. To overcome this basis for rejection, and in accordance with the suggestion made in the action, the words "to said human" have been added by amendment to the claim, immediately following the word "administration".

Claims 2-5 have been cancelled, rendering the rejection of these claims moot.

Claim 6-10 stand rejected 35 USC 112, second paragraph, because the expression "a human in need of such treatment" in claim 6 does not show which diseases, disorders or symptoms are treated by the use of the combination. To overcome this basis for rejection claim 6 has been amended so that it is now directed to a "method for treating HIV-1 infection in a human suffering from HIV-1 infection". This method is clearly taught by the specification. For the

sake of economy, the limitations that were in dependent claim 7 have been added to claim 6. Claim 7 has been cancelled, as it would otherwise be redundant.

Claims 1-15 have been cancelled, rendering the rejection of these claims moot.

Claim Rejections – 35 USC § 103

Claims 1, 6 and 8-10 stand rejected under 35 USC 103(a) as being unpatentable over Simoneau et al. (US 6,420,359) in view of Malaty et al. (Drug interactions of HIV protease inhibitors. *Drug Safety* 1999;20(2):147-169).

Simoneau et al. (the '359 patent) discloses the use of the compound of the formula I for the treatment of HIV infection. The difference between the claimed invention and the disclosure of the '359 patent is that the '359 patent does not disclose or suggest the co-administration of ritonavir with the compound of the formula I or the use of ritonavir in the claimed dosage range to achieve a reduction in the rate of metabolism of the compound of formula I.

It is respectfully urged that the secondary reference, Malaty et al., does not provide the motivation to modify the teaching of Simoneau et al. to yield the method of the present claims.

It is conceded that Malaty et al. teaches that ritonavir is a potent inhibitor of CYP 450 and that it can be used to increase the plasma concentration (AUC) of the non-nucleoside reverse transcriptase inhibitor efavirenz. However, the assertion that Malaty et al. teaches that ritonavir can be used to increase the plasma concentration (AUC) of the non-nucleoside reverse transcriptase inhibitor delaviridine is believed to be incorrect. In the table at page 155, Malaty et al. indicate that when ritonavir is co-administered with delaviridine the AUC of ritonavir is increased by 63% while no change in AUC of delaviridine is observed.

The applicant wishes to bring to the attention of the Office additional prior art references that describe the CYP 450-inhibiting property of ritonavir and that teach that ritonavir may be

used to improve the pharmacokinetics of drugs that are metabolized by CYP 450. For example, US Patents 6,037,157 and 5,635,523 describe the use of ritonavir for improving the pharmacokinetics of a wide variety of pharmaceutical agents, specifically including reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors.

To the knowledge of applicant, no prior art reference describes the use of ritonavir in combination with the compound of formula I.

For the reasons given below, it is earnestly believed that no secondary reference (specifically including, but not limited to, Malaty et al. and US Patents 6,037,157 and 5,635,523), provides the motivation to co-administer ritonavir with the compound of the formula I, in the manner now claimed.

Given the known ability of ritonavir to inhibit CYP 450 and thus improve the pharmacokinetics of pharmaceutical agents that are metabolized by CYP 450, it would be obvious to use ritonavir to improve the pharmacokinetics of a pharmaceutical agent that is known to be metabolized by CYP 450. That would be an obvious solution to a known or appreciated problem.

However, it is urged that there would be no *a priori* motivation to co-administer ritonavir with a pharmaceutical agent that is not known to be metabolized by CYP 450. There is never motivation to solve a problem that is not known to exist.

Identifying the previously unknown nature or source of a problem and then applying an obvious solution to the problem constitutes invention. See *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, (1923).

The present invention resides in the discovery that the compound of the formula I is subject to surprisingly rapid metabolism by the cytochromes P450, especially the CYP3A4 isoform. The fact that the compound of the formula I is so rapidly metabolized by cytochromes P450 was previously unknown. Prior to the making of the invention it had not been appreciated

that the metabolism of the compound of the formula I by cytochromes P450 is so rapid as to render it difficult to maintain therapeutically effective blood levels of the compound of the formula I. Put another way, the present invention resides in the recognition of the problem.

The invention provides a solution to this newly recognized problem. The solution, which is arguably obvious, but only after the problem has been discovered and is understood, is to improve the pharmacokinetics of the compound of the formula I by the co-administration of ritonavir, an inhibitor of CYP P450. When this is done, therapeutically effective blood levels of the compound of the formula I may readily be achieved. Inhibition of the enzymatic activity of CYP 450 serves to reduce the metabolism of the compound of formula I and thereby substantially improves the pharmacokinetics of the drug, so that less must be administered to attain therapeutic effect. Higher blood levels are also obtained.

In summary, the claimed invention is patentable over the prior art because the invention resides in the recognition of a previously unrecognized problem (that it is difficult to maintain therapeutically effective blood levels of the compound of the formula I) and in the recognition and appreciation of the source of the problem (that the compound of formula I is subject to rapid metabolism by CYP 450). The problem and source of the problem first came to be appreciated by the present applicant. This was the act of invention, not the discovery of the solution (co-administration of the CYP inhibitor ritonavir). Under the doctrine of *Eibel Process*, the applicant is deserving of a patent.

Respectfully submitted,

/Alan Stempel/
Alan Stempel Reg. # 28991

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
Tel.: (203) 798-4868